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CASE REPORT

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Detecting an Undiagnosed Case of Nonsyndromic Facial Dysmorphism Using Geometric Morphometrics

ABSTRACT: The Johns Hopkins University Center for Craniofacial Development and Disorders estimates that 1 in 3,000 children born in the United States is diagnosed with a rare form of craniosynostosis. Although the medical literature has documented numerous descriptions of craniofacial disorders from an anthropometric or genetic perspective, considerably fewer reports of these anomalies have been documented in the context of forensic anthropology. Similar genetic origins of many craniofacial anomalies generate ranges of phenotypic variation between and even within documented cases, producing difficulties in acquiring correct diagnoses. Identical physical characteristics manifested in different disorders create further complications in identifying a craniofacial syndrome in skeletal remains. Reported here is an unusual case of a possibly undiagnosed craniofacial abnormality in a set of identified skeletal remains from a North Carolina homicide case. Traditional metric and geometric morphometric approaches were utilized to further investigate morphological shape differences between the case study and a reference sample. Results show significant differences suggesting a nonsyndromic form of craniosynostosis.

KEYWORDS: forensic science, forensic anthropology, craniosynostosis, identification

Craniosynostoses are generally classified into syndromic (inherited) or nonsyndromic which are isolated and sporadic (1,2). Nonsyndromal forms of synostosis have been attributed to intrauterine compression of the cranium (3). Nearly 1 out of 3,000 children born in the United States suffers from a type of craniosynostosis, a condition caused by ''premature suture closure'' resulting in abnormal head form and other associated skeletal and soft tissue anomalies (4), and more than 700 hereditary disorders include craniofacial deformities (5). Although the prevalence of these conditions is relatively infrequent within the world population, syndromic and nonsyndromic forms of craniosynostosis and other craniofacial disorders have been widely reported in the medical literature. A vast majority of these cases, however, have been concerned with the identification, genetic testing, and anthropometric study of these anomalies in living individuals (6–14), with a particular focus on familial cases (15–21). Cephalometric studies have also been performed (22–25). Fewer reports (26–28) of craniofacial malformations have been documented in the forensic science literature.

The most recent studies of craniofacial abnormalities have primarily concentrated in the proper identification of each disorder for the development of surgical procedures and to obtain a more comprehensive assessment of their common genetic origins (6–8,13,29,30). In particular, genetic research on syndromic forms of craniosynostosis has increasingly focused on comparing the underlying genetic mutations of each form with the consideration that little phenotypic variation exists between them (6–8,13). The genetic similarities between these disorders resulting from mutations on the same genes generate complications in correctly identifying them based on physical characteristics alone, sometimes leading to misdiagnosis (6–8,13,19). The amount of phenotypically expressed homogeneity existing between syndromic craniosynostoses, however, is merely one of the challenges confronting medical professionals. Variation in type and severity of physical manifestations is also present within each individual craniofacial disorder, which creates further barriers in establishing correct diagnoses (9–21). Overlapping phenotypically expressed traits produces uncertainty among medical personnel in diagnosing patients; however, properly identifying these disorders in skeletal remains, particularly in a forensic setting, is significantly more problematic. Here, we report on an atypical case of a possibly undiagnosed nonsyndromic craniofacial abnormality in a set of identified skeletal remains from a North Carolina homicide case.

Autopsy and Anthropological Findings

In August 1992, the partially skeletonized and mummified remains of a White, 31-year-old female were discovered in a vacant, dilapidated house in North Carolina. At autopsy, cause of death was determined to be blunt force trauma to the left lateral portion of the skull and manner of death was reported as homicide. Examination of the dry skull indicated perimortem fracturing of the left zygomatic, the left maxillary region, the nasals, and the upper left and right central and lower right lateral incisors (Fig. 1), consistent with blunt force trauma. The remains showed evidence of a mild form of *spina bifida occulta* of the posterior sacrum with the sacral hiatus longer than expected. Craniofacially, the midface and palate appear atypically narrow and underdeveloped (Fig. 2). However, the vault appears normal. The upper left and right lateral incisors, lower right canine, and lower left and right second premolars are absent, possibly congenitally, and prior orthodontic treatment was obvious, indicating that the treatment may have been performed to correct dental irregularities associated with the narrow palate. The decedent was positively identified through antemortem

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FIG. 1—*Anterior view of 31-year-old White female.*

FIG. 2—*Inferior view of 31-year-old White female.*

dental records; however, the atypical cranial features and the postcranial anomalies were not documented by the medical examiner.

Metric and Geometric Morphometric Analyses

The nasal (nasal breadth × 100/nasal height) and maxilloalveolar (maxilloalveolar breadth × 100/maxilloalveolar length) indices were calculated. The Nasal Index (36.17) places the decedent in the exceedingly narrow nasal aperture range, while the Maxilloalveolar Index (104.44) places her in the very long or narrow palate range.

To further evaluate shape differences, *x*, *y*, and *z* coordinates of 13 standard craniofacial landmarks (Table 1) were used to compare our case study to a sample of clinically normal White females (n = 16) from the W. M. Bass Donated Collection. Only right dacryon, ectoconchion, and zygomaxillary were included as the corresponding left sides were missing in our case study because of trauma. A generalized Procrustes analysis (GPA) was used to bring all specimens into a common coordinate system. The GPA

TABLE 1—*List of landmarks*

Landmark	Side
1. Alveolon	Midline
2. Basion	Midline
3. Dacryon	Right
4. Ectomalare	Right/Left
5. Ectoconchion	Right
6. Frontomalare Anterior	Right/Left
7. Nasion	Midline
8. Opisthion	Left
9. Prosthion	Midline
10. Subspinale	Midline
11. Zygomaxillare	Right

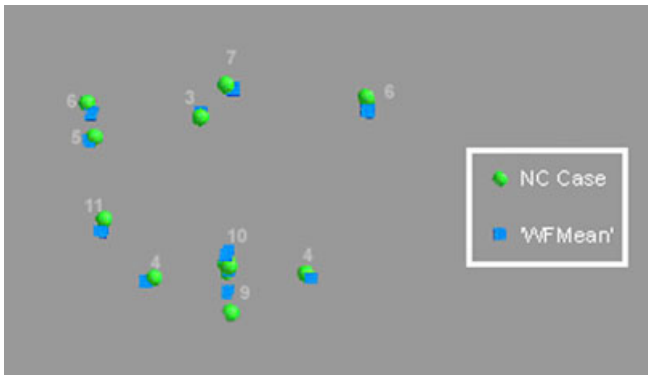

FIG. 3—*Superimposition of the case study (green spheres) and mean landmark locations of clinically normal White females (blue squares). See Table 1 for landmark identification.*

superimposition was performed using the program Morpheus et al., written by Slice (31). The superimposed coordinates (or shape variables) were then utilized in the subsequent multivariate analyses. A principal component analysis of the covariance matrix was conducted on the shape variables to reduce the dimensionality of the data or as a variable reduction procedure, to meet the requirements of the parametric test. The degree of differentiation among the groups (case study: White female sample and White female group mean) was evaluated using Mahalanobis D^2. The multivariate analyses were conducted using the SAS system for Windows Version 9.1.3 (SAS Institute Inc., Cary, NC) (32).

Figures 3 and 4 depict the anterior and lateral views of the superimposition of the case study (green spheres) and White female group mean (blue squares) illustrating the morphological difference between our NC case study and the White female consensus configuration or group mean. Left frontomalare anterior and

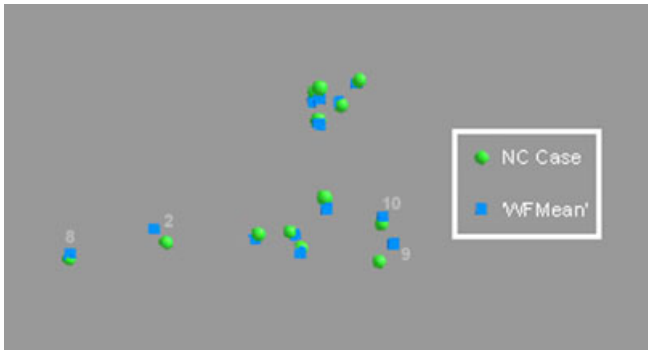

FIG. 4—*Lateral view of superimposition. See Table 1 for landmark identification.*

TABLE 2—*Mahalanobis* D^2.

Group	Case Study	White Female	White Female Mean
Case study	0	0.05	0.20
White female	23.890	0	1.0
White female mean	23.892	0.002	0

Upper diagonal *p*-values and lower diagonal distances.

zygomaxillare are more superiorly oriented, left ectoconchion is more medially placed, basion and opisthion are more inferiorly oriented, subspinale and prosthion are more inferiorly oriented, and alveolon is more superiorly placed in the case study. The Mahalanobis D^2 distances based on the first five principal component scores are presented in Table 2 and demonstrate the dissimilarity between the case study and the sample of clinically normal White females.

Discussion

According to the Johns Hopkins University Center for Craniofacial Development and Disorders, an estimated 1 in 3,000 cases of craniosynostosis are reported every year (4), with craniofacial abnormalities comprising *c.* 1 in 700 hereditary disorders in the United States (5). Additionally, the National Institute of Child Health and Human Development estimates that nearly 1 in 800 births in the United States results in Down's syndrome annually (33). Syndromic craniosynostoses account for significantly fewer cases of craniofacial deformities (4). Cases of craniosynostosis and other craniofacial abnormalities with similar physically expressed traits, including Down's syndrome, are well described in the medical literature. Known cases of these types of anomalies in a forensic context are significantly less common (26–28), possibly because of the difficulty in distinguishing between these disorders in skeletal remains.

Anthropometric and genetic studies of craniofacial abnormalities frequently appear in the literature, most likely because of an increasing need to develop successful surgical procedures and understand the complex genetic origins shared by multiple craniofacial disorders (6–8,13,29,30). Numerous case studies have demonstrated that several types of syndromic craniosynostosis result from analogous mutations on the same genes (6–8,10,15), which causes uncertainty in diagnosing patients, particularly when several physical manifestations are shared between these disorders (6–8). Tsukahara et al. (15) documented a case of a 4.5-year-old child with clinical manifestations of Pfeiffer and Saethre–Chotzen syndromes, suggesting that the child probably suffered from "a transitional form" between the two craniosynostotic disorders. In particular, studies concerning the underlying genetics of syndromic forms of craniosynostosis propose that these disorders result from the same mutations on a set of genes known as "fibroblast growth factor receptors" (FGFR) genes (6–8,13). Nuckolls et al. (13) report that mutations on the FGFR2 gene cause Apert, Crouzon, Antley-Bixler, Saethre-Chotzen, Jackson-Weiss, Beare-Steveson, and Pfeiffer syndromes. The significance of this research is even more valuable when considering that earlier research defined these disorders solely on physical characteristics (7).

Although the same mutations on the sets of genes known as FGFR's result in different disorders, causing these syndromes to exhibit some homogeneity in their phenotypically expressed traits (6–8,13), differentiation *between* disorders is not the sole problem. Properly diagnosing an individual with one of these disorders is further complicated by the fact that not all individuals manifest the same level of severity or in some cases, the same types of symptoms (9–25). This has been increasingly demonstrated in familial studies of craniosynostoses (14–21), although relatedness between individuals is not a factor in the expression of phenotypic variation within individual disorders. Jackson et al. (19), Bianchi et al. (16), Saldino et al. (20), Al-Qattan and Phillips (14), Altintas et al. (17), and Flippen (18) have documented familial cases of several syndromic craniosynostoses in which closely related family members exhibited variation in phenotypically expressed symptoms in both type and severity. Familial and nonfamilial studies have both demonstrated that variability in clinical manifestations exists between and within these disorders (9–25,34). Kreiborg and Pruzansky (23) and Kreiborg and Björk (35) have described Crouzon's syndrome patients as exhibiting "brachycephaly with increased cranial height" with some individuals demonstrating "varying degrees of maxillary hypoplasia, increased anterior face height, posterior inclination of the mandible, and relative prognathism of the mandible with severe malocclusion." Similarly, Peterson and Pruzansky (36) have described Apert's syndrome patients exhibiting "hypoplasia of the middle third of the face, including the maxilla…and relative prognathism." Shapiro et al. (37) have described individuals with Down's syndrome, a chromosomal disorder, as suffering from "short stature, brachycephaly, hypoplasia of mid-face bones, pelvis anomalies, and numerous other skeletal maldevelopments"—some features which are obviously comparable with those of syndromic craniosynostoses.

The relative physical variation present between forms of syndromic craniosynostosis requires medical physicians to utilize a combination of genetic testing and examination of physical traits to correctly distinguish between these disorders in living individuals. The overlapping physical characteristics present among these abnormalities, however, creates further difficulties in identifying a particular syndrome in skeletal remains, because of the absence of soft tissue, when several soft tissue or organ-based deformities are relied upon by physicians in establishing a correct diagnosis (9–21). This is particularly true in relation to syndromic forms of craniosynostosis which often exhibit "soft-tissue syndactyly of the hands or feet," but may or may not lack fusion of the bones (7,8). Some skeletal manifestations of Crouzon's, Apert's, Pfeiffer's, Down's syndrome, and other disorders are: "maxillary hypoplasia" (36–41), "a high-arched and narrow palate" (36–41), "brachycephaly" (36–41), orthodontic abnormalities (36–41), a narrow nasal opening (36–41), and "shallow eye orbits" (36–41)—all features expressed in the skull of the case study that we present here. The overlap in these particular characteristics between the afore-mentioned craniofacial disorders, however, generates difficulties in diagnosing the decedent based solely on morphological characteristics, thus, warranting a three-dimensional metric study of the skull for comparison of obtained craniofacial measurements to those of previous research studies.

One of the rarer forms of nonsyndromic synostosis is premature fusion of the metopic suture accounting for 3–4% of all synostosis or *c.* 04–1 per 1,000 live births (2,42–44). The metopic suture begins to fuse after the first year and is usually completely obliterated by the seventh year (3). The early fusion of this suture in comparison with other cranial sutures may account for the lower reported prevalence. In the infant, metopic synostosis is characterized by deformities of the upper face and anterior neurocranium including a trigonocephalic skull shape, metopic suture ridge, narrow interobital distance, narrow forehead, hypotelorism, and deficient orbital rims (2,44). However, most of these characteristics have only been described in infants and children and not in the

adult. There are several contradicting studies regarding the self-correcting nature of the deformity. Dominguez et al. (45) found that in 15 untreated individuals, the frontal keel and hypertolerism disappeared. The traditional metric and geometric morphometrics analyses used in this case study show significant differences in the craniofacial form between our case study and the clinically normal sample. Weber et al. (46) compared the morphometrics of 40 normal adult skulls to 42 adult skulls that exhibited several forms of craniosynostosis. Although only two trigonocephalic skulls were available for analysis, the measurements that were taken indicated that the "maximum cranial breadths" of these individuals were higher than the mean cranial breadth for the normal skulls; however, these two individuals fell within the range of the 40 normal adult skulls for "maximum cranial breadth" (46). The mean "maximum cranial breadths" for the trigonocephalic skulls were "15.3 and 14.6 cm," compared to the mean "maximum cranial breadth" of "14.0 cm" for the normal skulls. For "length of metopic suture," one of the abnormal skulls fell outside of the range of normal variation for this measurement (46). Additionally, metric analyses were performed on scaphocephalic, plagiocephalic, oxycephalic, and brachycephalic skulls. Weber et al. (46) determined that "the mean cranial length was 12% greater in adult scaphocephaly." Although for most of these measurements, the malformed skulls fall into the measurement ranges of the normal skulls, the mean measurements for all of these cranial deformities were either lower or higher than those of the normal adult skulls, indicating that to some degree a morphometric difference between normal and craniosynostotic skulls can be determined.

The absence of postcranial deformities usually associated with syndromic craniosynostosis would appear to suggest a probable sporadic nonsyndromic form of metopic synostosis as an explanation for the atypical frontal and facial narrowness observed in our case study. These results suggest that the identification of and differentiation between related craniofacial abnormalities in skeletal remains is difficult and necessitates further research. Few accounts (26–28) of craniosynostosis have been reported in the forensic anthropological literature, most likely because of the rarity of these skeletal malformations. One report (26) indicates that craniosynostotic conditions can generate difficulties in accurately establishing sex and ancestry in some forensic cases, although the individual, who was determined to have scaphocephaly, was eventually positively identified. Despite the infrequency of these conditions among the human population, geometric morphometric and traditional morphometric analyses of skulls exhibiting craniofacial abnormalities and comparisons to normal skulls would be beneficial to forensic anthropologists in establishing identification of individuals who may otherwise remain unidentified, particularly, if the correct determination of sex and ancestry is difficult in some cases because of these types of craniofacial malformations.

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